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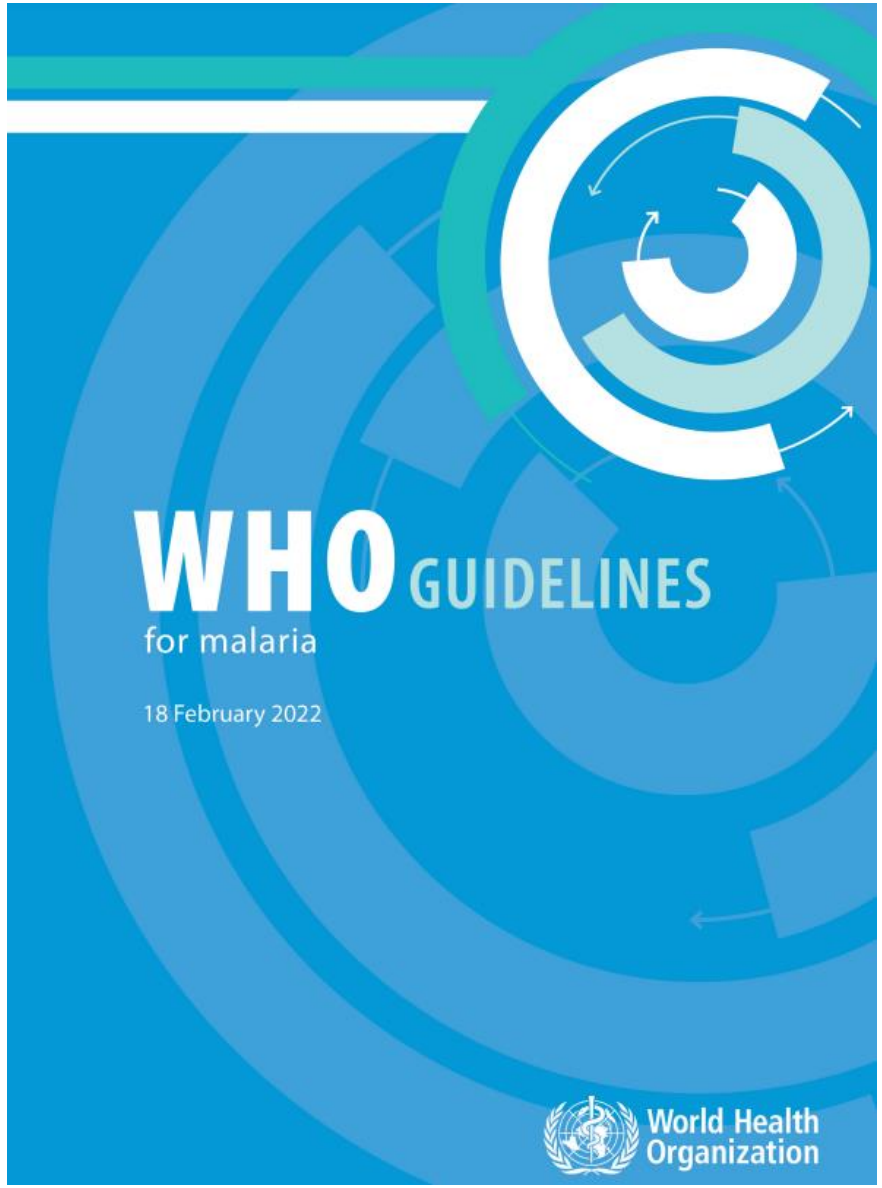
First-trimester treatment with artemisinin derivatives versus non-artemisinin antimalarials and the risk of adverse pregnancy outcomes in Africa and Asia: Updated individual patient data meta-analysis

Saito M., McGready R., Tinto H., Rouamba T., Mosha D., Rulisa S., Kariuki S., Desai M., Manyando C., Njunju E.M., Sevene E., Vala A., Augusto O., Clerk C., Were E., Mrema S., Kisinza W., Byamugisha J., Kagawa M., Singlovic J., Yore M., van Eijk A., Mehta U., Stergachis A., Hill J., Stepniewska K., Gomes M., Guerin P., Nosten F., ter Kuile F.O., Dellicour S.

RBM Malaria in Pregnancy Working Group Annual Meeting, 13 September 2022

Background



2nd & 3rd trimester

- ACTs (3 days) since 2006
- Quinine + clindamycin (7d, if ACTs not available)

1st trimester

- Quinine + clindamycin (7d)
- Artemisinins not recommended unless
  - severe disease
  - no other drugs available
  - rescue therapy (i.e. quinine failures)

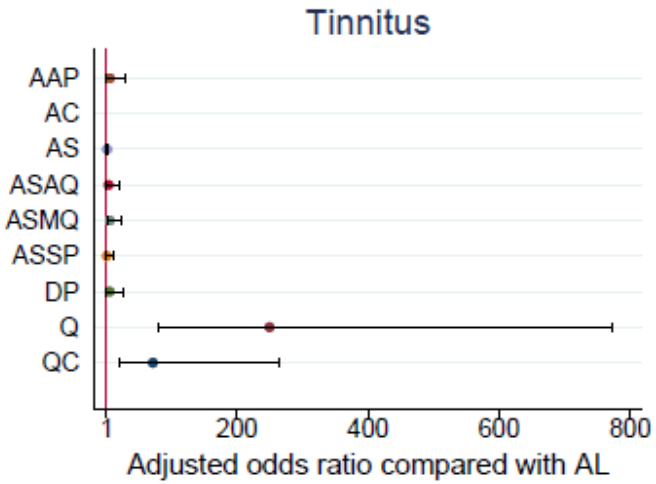
WHO Review of evidence on artemisinin safety in pregnancy

- WHO reviews:
  - 2 informal consultations 2002 and 2006
    > insufficient evidence to change policy recommendations.
  - Evidence Review Group and Malaria Policy Advisory Committee Meetings in 2015
    > recommended update to include ACT as an option in 1st trimester but not implemented.

Research in context

ACTs	Quinine + Clindamycin
• Shorter treatment course (3 vs 7 days for quinine) • Better tolerated • Longer post-treatment prophylaxis • Better gametocidal property -> reduce onwards transmission • Better efficacy (demonstrated in 2nd/3rd trimester & non-pregnant populations)	• Not well tolerated • Lengthy and complex treatment regimen (8-hourly for 7 days) • Poor adherence and treatment failure • Quinine monotherapy mostly used • Only used for 1st trimester population

2nd/3rd trimester, PCR corrected treatment failure risk for quinine vs AL : adjusted HR 6.11 (95%CI: 2.57–14.54)



From Saito et al 2020 Lancet Inf Dis, 20(8)

Study aim

To compare the risk of adverse pregnancy outcomes between artemisinin-based (ABT) and non-artemisinin treatment (non-ABT) of malaria in the 1st trimester and the suggested artemisinin embryo-sensitive period

Study Design and Methods

- Updated systematic review and individual patient data (IPD) meta-analysis
- Study inclusion
  - Confirmed artemisinin exposures in 1st trimester
  - Prospective follow up
  - Internal comparison group
- Participant inclusion
  - Excluded if gestational age measurement missing
  - Excluded multiple gestation pregnancies
  - Included only viable pregnancies as assessed prior to treatment (SMRU)
  - Included regardless of parasitological confirmation, severity or parasite species
  - Cases censored at time of exposure to SP, unconfirmed antimalarials or exposure to both ABT and non-ABT in the first trimester

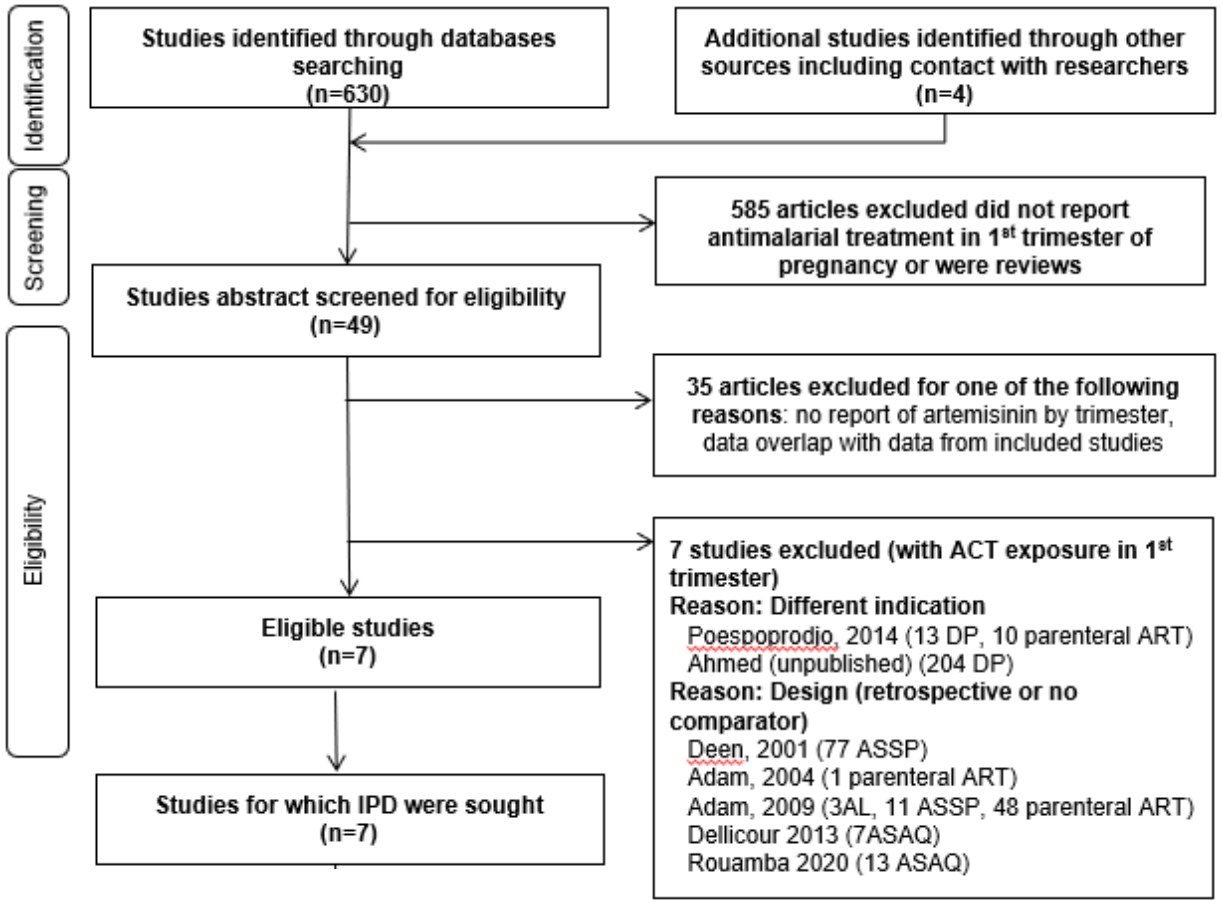
Statistical analysis

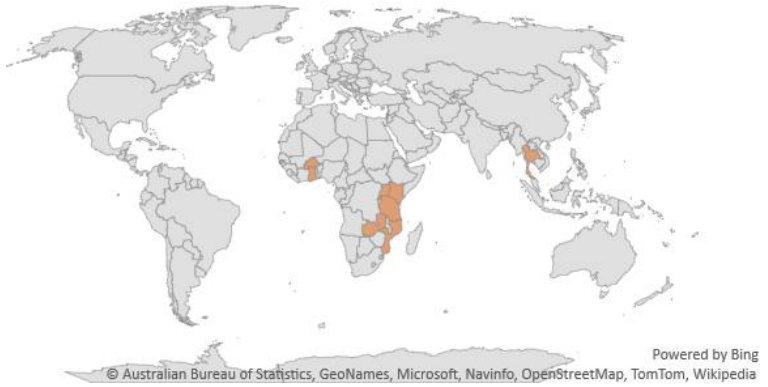
- Primary analysis: ABT vs non-ABT
- Subgroup analysis: specific ACT vs quinine
- IPD: 1-stage random-effects adjusting for clustering by study site
- Cox regression with shared frailty
  - Gestational week as the time scale
  - Left truncated
  - Right censoring
  - Exposure time-dependant
- Sensitivity analyses
  - E-values to assess potential unmeasured confounding
  - Using unexposed comparison group
  - Assessing smaller exposure risk-windows
  - Inclusion of unconfirmed exposures
  - Different statistical models
  - Multiple imputations of missing data

An E-value is the minimum risk ratio that an unmeasured confounder would need to have with the outcome and ABT-exposure to unmask an increased risk of adverse outcome in the women who were exposed to ABT (i.e., for the lower confidence interval to shift over the null, HR>1)

Results

Result- Literature Search





7 included studies (12 cohorts) with 1st trimester artemisinin data

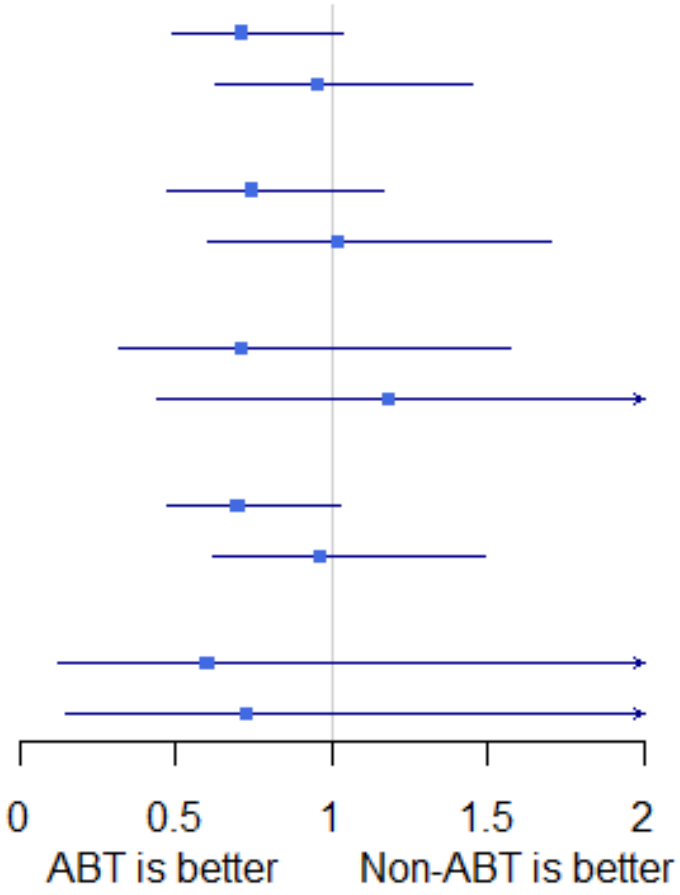
- 6 studies from Africa and 1 from Asia
- 34,178 pregnancies
  - 1,813 (5%) confirmed antimalarial in 1st trimester
  - 737 (2%) ABT: 74% Africa & 71% AL
  - 1,076 (3%) non-ABT: 25% Africa & 85% Quinine

Addition to 2017 review:

- 8,126 pregnancies
- 60 ABT 1st trimester exposures
- 309 non-ABT 1st trimester exposures

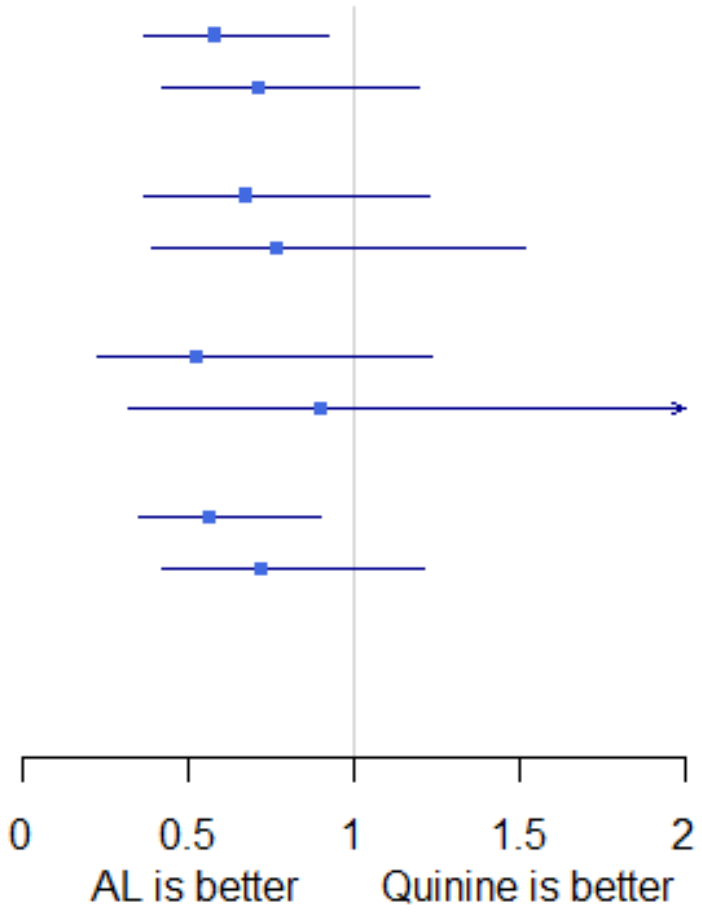
Result- Artemisinin vs non-Artemisinin

Outcome	Number ABT	Non-ABT	aHR (95%CI)	p-value	E-value
Composite outcome					
First trimester	42/736	96/1074	0.71 (0.49-1.03)	0.071	3.54
Embryo-sensitive period	37/584	60/822	0.95 (0.63-1.45)	0.828	2.60
Miscarriage					
First trimester	27/669	76/1070	0.74 (0.47-1.17)	0.195	3.71
Embryo-sensitive period	23/533	46/818	1.02 (0.61-1.70)	0.951	2.72
Stillbirth					
First trimester	13/646	12/743	0.71 (0.32-1.57)	0.395	5.79
Embryo-sensitive period	12/518	6/608	1.18 (0.44-3.18)	0.746	4.05
Fetal loss					
First trimester	40/736	88/1074	0.70 (0.47-1.02)	0.065	3.68
Embryo-sensitive period	35/584	52/822	0.96 (0.62-1.49)	0.861	2.64
Major congenital anomaly					
First trimester	2/736	8/1074	0.60 (0.13-2.87)	0.521	15.64
Embryo-sensitive period	2/584	8/822	0.72 (0.15-3.49)	0.688	12.89



Result- Artemether-Lumefantrine vs Quinine

Outcome	Number AL	Quinine	aHR (95%CI)	p-value	E-value
Composite outcome					
First trimester	25/524	84/915	0.58 (0.36-0.92)	0.021	4.98
Embryo-sensitive period	22/445	51/684	0.71 (0.43-1.20)	0.200	4.17
Miscarriage					
First trimester	15/464	68/913	0.67 (0.37-1.23)	0.196	4.89
Embryo-sensitive period	12/398	40/682	0.77 (0.39-1.52)	0.445	4.65
Stillbirth					
First trimester	10/488	12/590	0.53 (0.22-1.24)	0.142	8.47
Embryo-sensitive period	10/415	6/469	0.90 (0.32-2.51)	0.841	5.71
Fetal loss					
First trimester	25/524	80/915	0.56 (0.35-0.90)	0.016	5.18
Embryo-sensitive period	22/445	46/684	0.72 (0.42-1.21)	0.214	4.20
Major congenital anomaly					
First trimester	0/524	4/915	No events	NA	NA
Embryo-sensitive period	0/445	5/684	No events	NA	NA



Result- Congenital anomalies

Congenital anomaly subgroup	First trimester			Embryo-sensitive period	
	ABT (n=623)	Non ABT (n=681)	Unexposed (n=26270)	ABT (n=503)	Non ABT (n=558)
Any major congenital anomaly	2* (0.32%)	8 (1.17%)	182 (0.69%)	2** (0.40%)	8 (1.43%)
Cases with multiple congenital anomalies	0 (0%)	1 (0.15%)	36 (0.14%)	0 (0%)	1 (0.18%)
Nervous system	0 (0%)	0 (0%)	27 (0.10%)	0 (0%)	0 (0%)
Eye	0 (0%)	0 (0%)	8 (0.03%)	0 (0%)	0 (0%)
Ear, face and neck	0 (0%)	0 (0%)	13 (0.05%)	0 (0%)	0 (0%)
Congenital heart defects	0 (0%)	1 (0.15%)	15 (0.07%)	0 (0%)	1 (0.18%)
Oro-facial clefts	1 (0.16%)	2 (0.29%)	30 (0.12%)	0 (0%)	2 (0.36%)
Digestive system	0 (0%)	0 (0%)	20 (0.08%)	1 (0.20%)	0 (0%)
Abdominal wall defects	0 (0%)	0 (0%)	10 (0.04%)	0 (0%)	0 (0%)
Urinary	0 (0%)	0 (0%)	4 (0.02%)	0 (0%)	0 (0%)
Genital	0 (0%)	0 (0%)	8 (0.03%)	0 (0%)	0 (0%)
Limb	1 (0.16%)	5 (0.73%)	46 (0.18%)	1 (0.20%)	5 (0.90%)
Other anomalies / syndromes	0 (0%)	1 (0.15%)	24 (0.10%)	0 (0%)	1 (0.18%)
Cases with anomalies excluded from EUROCAT subgroups	0 (0%)	0 (0%)	3 (0.01%)	0 (0%)	0 (0%)

*1 case of cleft lip and palate and 1 case of bilateral syndactyly.
** 1 case of bilateral syndactyly and 1 case imperforated anus.

Studies were not designed to systematically screen and detect congenital heart defects.

Strengths and Limitations

Limitations

- Limited data on potential confounders
- Potential confounding by indication
- Potential for exposure misclassification
- No data on dosage
- Limited statistical power for specific ACTs other than AL
- Misclassification of miscarriage
- Statistical heterogeneity not assessed
- Congenital heart defects not assessed systematically

Strengths

- All identified eligible studies contributed IPD
- Prospective design and exposure confirmation
- High E-values indicating low risk for residual confounding
- The results were robust across sensitivity and sub-group analyses

Conclusions

- No difference in risk of stillbirth, miscarriage or major congenital anomalies in confirmed ABT exposure vs non-ABT antimalarials considered safe in the 1st trimester
  - excludes a 1.03-fold and 1.45-fold increase in adverse pregnancy outcomes with ABT vs non-ABT in the 1st trimester and embryo-sensitive period
- 1st trimester AL Rx associated with a 42% lower risk of adverse pregnancy outcomes compared to quinine (aHR: 0.58, 95%CI 0.36- 0.92)
- The benefit-risk favours the use of AL over quinine for confirmed malaria in the 1st trimester of pregnancy based on the evidence for safety, efficacy, tolerability, and adherence
- Targeted surveillance needed to be able to detect signals for specific congenital anomalies

Acknowledgements

- All study participants and study teams
- IPD contributors and co-authors
- Birth Defect Panel set up for the WHO Pregnancy Registry pilot studies
- Funders of meta-analysis: Medicines for Malaria Venture (MMV) and the World Health Organization (WHO)

Thank you

Back up slides

Definitions

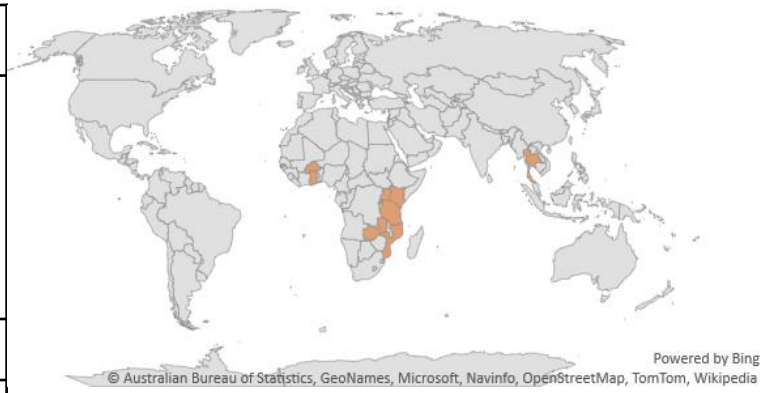
- Antimalarial exposures*:*
  - 1st trimester: 2-13 weeks (inclusive) post-LMP
  - Artemisinin embryo-sensitive period: 6-12 weeks (inclusive) post-LMP
  - Exposures confirmed by >=2 data sources and/or medical record
  - Unexposed: no antimalarials up to 14 weeks
- Outcome:
  - Primary: composite endpoint including miscarriage, stillbirth and major congenital anomalies
  - Miscarriage: confirmed pregnancy which ended <28 weeks gestation
  - Stillbirth: stillborn infant from confirmed pregnancy at >=28 weeks gestation
  - Major congenital anomalies: any structural abnormality with surgical, medical or cosmetic importance that is present at birth detected by surface examination
    - Events included according to WHO Birth Defect Panel criteria on minor and major defects

WHO Birth Defect Panel criteria for congenital anomalies

- Anomalies that do not constitute “major congenital anomalies”, plus hereditary and chromosomal disorders that are known not to be caused by exposure to drugs, are excluded from the primary analysis
- The following features/anomalies will therefore be excluded from the congenital malformations endpoint of assessing drug-related risk:
  - minor anomalies (e.g. transverse palmar crease)
  - normal variations that have no cosmetic or functional significance (e.g. umbilical hernia in African infants)
  - hereditary disorders (e.g. polydactyly postaxial Type B)
  - birth marks (e.g. haemangiomas; congenital moles)
  - chromosome abnormalities (e.g. Down syndrome)
  - positional deformities that do not require casting or surgery will not be included (e.g. congenital hip dislocation in infants who are born in breech position)
  - features of prematurity (e.g. undescended testes and patent ductus arteriosus in infants less than 37 weeks gestational age)
  - biochemical abnormalities (e.g. carriers of cystic fibrosis, and abnormal haemoglobins that may be identified during newborn screening).

Result- Description of included studies

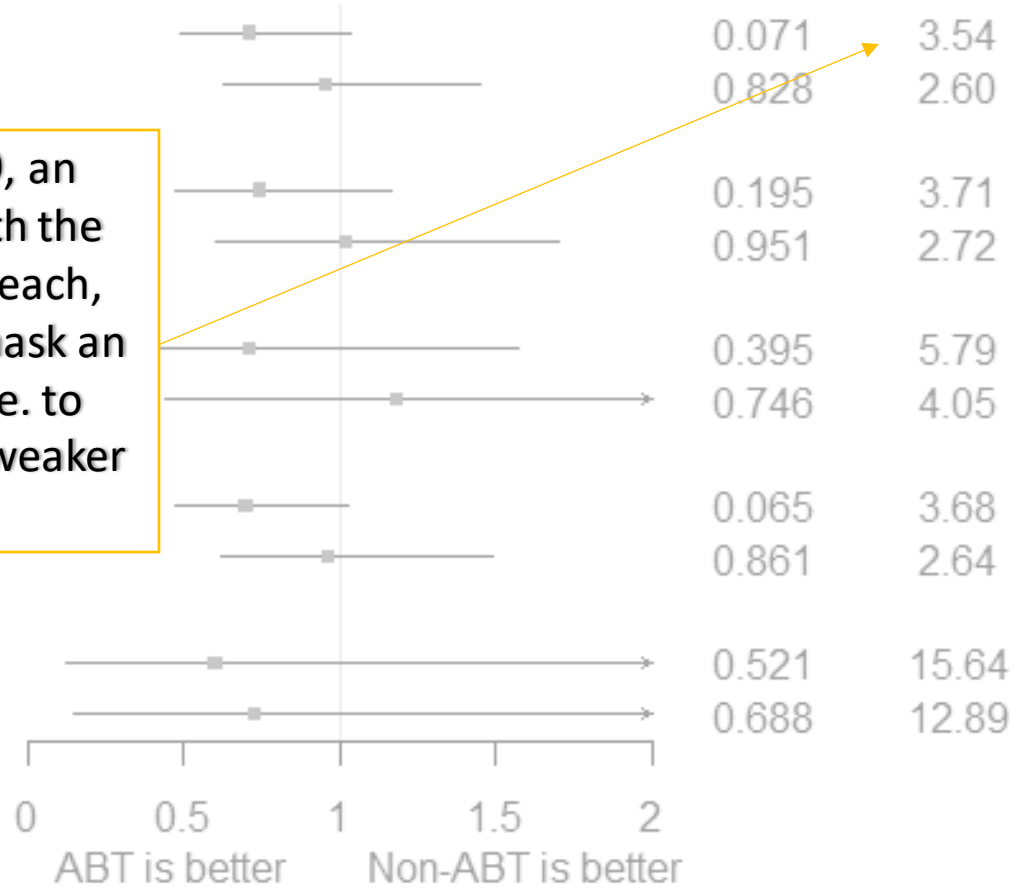
Study	Country	Study period	Mean gestational week at enrolment (SD)	First-trimester exposures		
				No. confirmed ABT	No. confirmed non-ABT	No. Unexposed to antimalarial
Rouamba	Burkina Faso	2012-2015	16.9 (6.6)	13	152	4354
WHO TDR	Ghana	2010-2011	15.6 (6.8)	5	4	246
	Kenya	2010-2011	25.2 (3.9)	3	3	230
	Tanzania	2010-2011	18.1 (6.5)	0	0	187
	Uganda	2011-2012	26.9 (6.7)	3	3	171
Mosha	Tanzania	2012-2013	14.7 (3.5)	156	69	1527
Dellicour	Kenya	2011-2013	15.9 (9.9)	71	2	1075
Sevene	Mozambique	2011-2013	21.0 (5.7)	19	5	710
Tinto	Burkina Faso	2011-2013	24.0 (6.2)	30	21	626
Rulisa	Rwanda	2007-2009	28.0 (7.5)	77	0	1571
Manyando	Zambia	2004-2008	24.8 (8.0)	166	6	763
McGready	Thailand	2000-2017	9.1 (2.6)	194	811	20905
Overall				737	1076	32365



Result- Artemisinin vs non-Artemisinin

Outcome	Number ABT	Non-ABT	aHR (95%CI)	p-value	E-value
Composite outcome					
First trimester	42/736	96/1074	0.71 (0.49-1.03)	0.071	3.54
Embryo-sensitive period	37/584	60/822	0.95 (0.63-1.45)	0.828	2.60
Misca					
First				0.195	3.71
Emb				0.951	2.72
Stillbir					
First				0.395	5.79
Emb				0.746	4.05
Fetal l					
First				0.065	3.68
Embryo-sensitive period	35/584	52/822	0.96 (0.62-1.49)	0.861	2.64
Major congenital anomaly					
First trimester	2/736	8/1074	0.60 (0.13-2.87)	0.521	15.64
Embryo-sensitive period	2/584	8/822	0.72 (0.15-3.49)	0.688	12.89

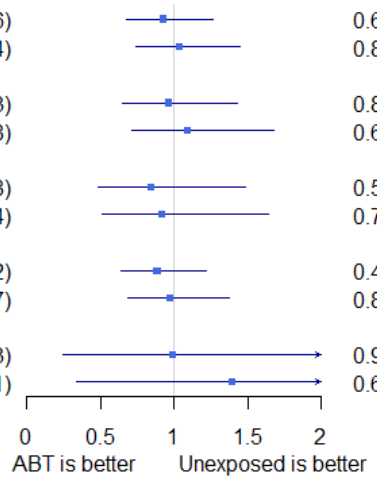
With an observed risk ratio Lower limit CI of RR=0.49, an unmeasured confounder that was associated with both the outcome and the exposure by a risk ratio of 3.54-fold each, above and beyond the measured confounders, could mask an increased risk with a true lower limit of CI above 1 (i.e. to move the confidence interval to exclude the null), but weaker confounding could not



Sensitivity analysis- comparison to unexposed

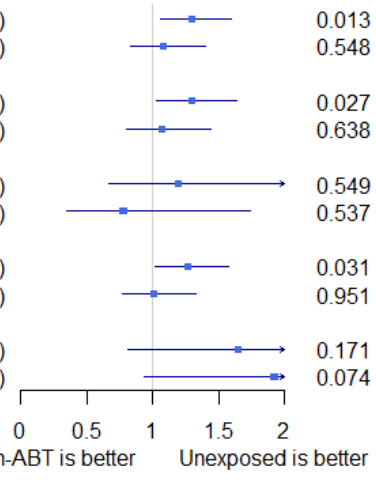
ABT

Outcome	Number Exposed	Unexposed	aHR (95%CI)	p-value	E-value
Composite outcome					
First trimester	42/736	2393/32203	0.92 (0.67-1.26)	0.617	2.36
Embryo-sensitive period	37/584	2454/32781	1.03 (0.74-1.44)	0.849	2.07
Miscarriage					
First trimester	27/669	1807/30176	0.96 (0.65-1.43)	0.853	2.49
Embryo-sensitive period	23/533	1859/30721	1.09 (0.71-1.68)	0.692	2.20
Stillbirth					
First trimester	13/646	404/27847	0.84 (0.48-1.48)	0.556	3.63
Embryo-sensitive period	12/518	412/28325	0.91 (0.51-1.64)	0.762	3.39
Fetal loss					
First trimester	40/736	2211/32203	0.88 (0.64-1.22)	0.447	2.54
Embryo-sensitive period	35/584	2271/32781	0.97 (0.69-1.37)	0.863	2.30
Major congenital anomaly					
First trimester	2/736	182/32203	0.99 (0.24-4.03)	0.984	7.84
Embryo-sensitive period	2/584	183/32781	1.39 (0.34-5.71)	0.647	5.41

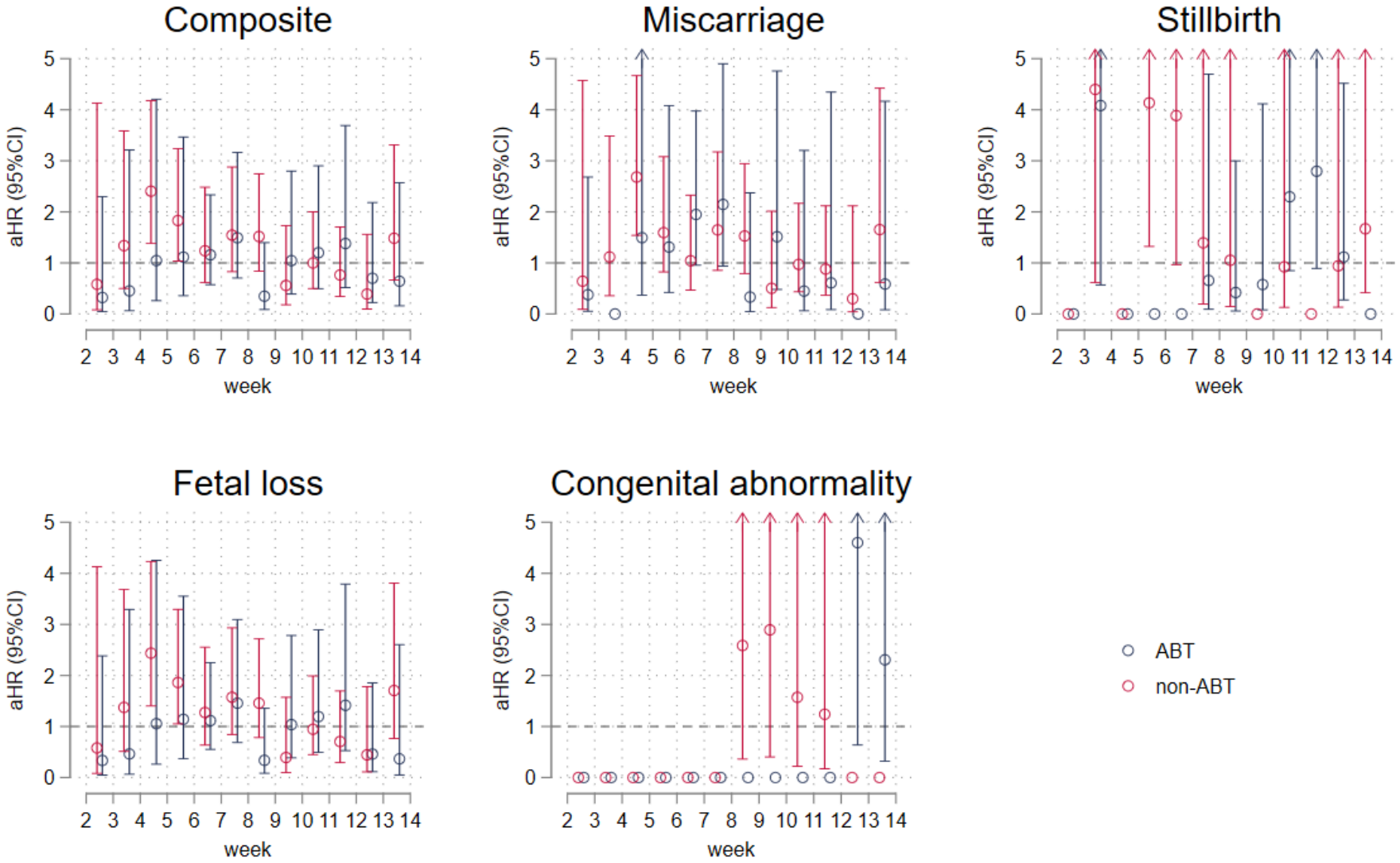


Non ABT

Outcome	Number Exposed	Unexposed	aHR (95%CI)	p-value	E-value
Composite outcome					
First trimester	96/1074	2393/32203	1.30 (1.06-1.60)	0.013	NA
Embryo-sensitive period	60/822	2454/32781	1.08 (0.84-1.40)	0.548	1.71
Miscarriage					
First trimester	76/1070	1807/30176	1.30 (1.03-1.64)	0.027	NA
Embryo-sensitive period	46/818	1859/30721	1.07 (0.80-1.44)	0.638	1.84
Stillbirth					
First trimester	12/743	404/27847	1.19 (0.67-2.12)	0.549	2.38
Embryo-sensitive period	6/608	412/28325	0.78 (0.35-1.74)	0.537	5.30
Fetal loss					
First trimester	88/1074	2211/32203	1.27 (1.02-1.57)	0.031	NA
Embryo-sensitive period	52/822	2271/32781	1.01 (0.77-1.33)	0.951	1.97
Major congenital anomaly					
First trimester	8/1074	182/32203	1.65 (0.81-3.36)	0.171	1.82
Embryo-sensitive period	8/822	183/32781	1.92 (0.94-3.92)	0.074	1.36



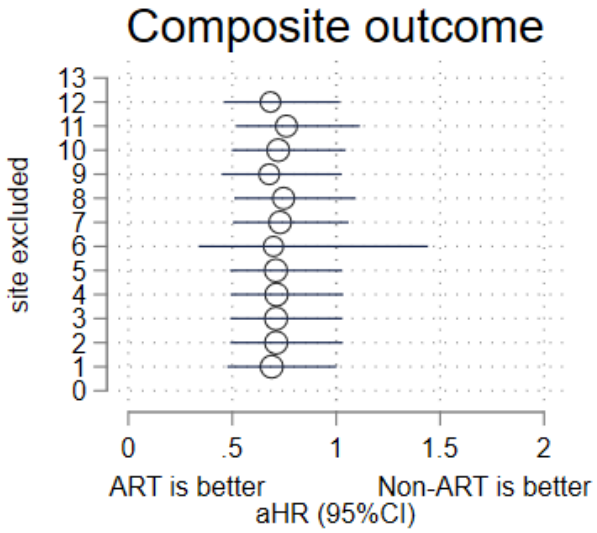
Sub-group analysis- assessment of exposure risk window

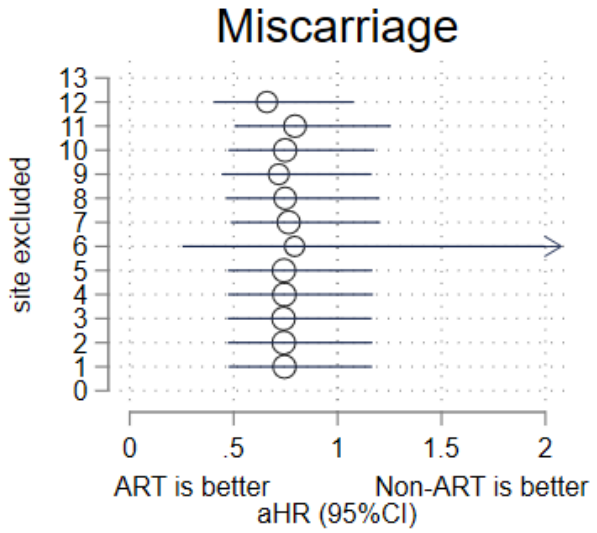


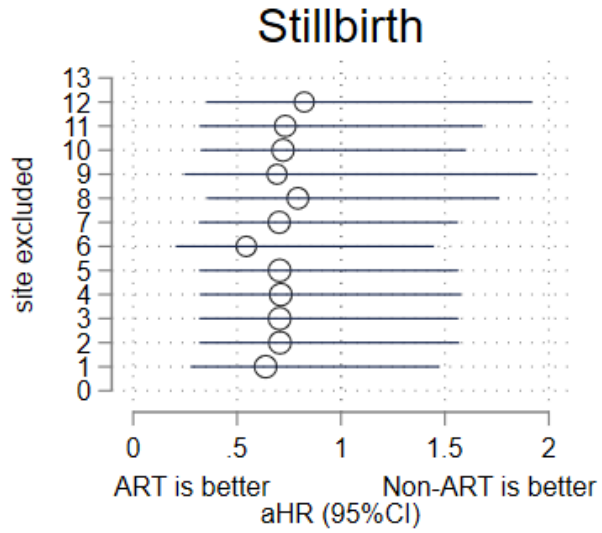
Numbers of women for the composite outcome													
week	2	3	4	5	6	7	8	9	10	11	12	13	
ABT	1/27	1/22	2/27	3/29	8/97	7/75	2/89	4/75	5/74	4/56	3/84	2/81	
non-ABT	1/18	4/34	13/69	12/76	8/94	10/101	11/122	3/92	8/135	6/131	2/104	6/94	

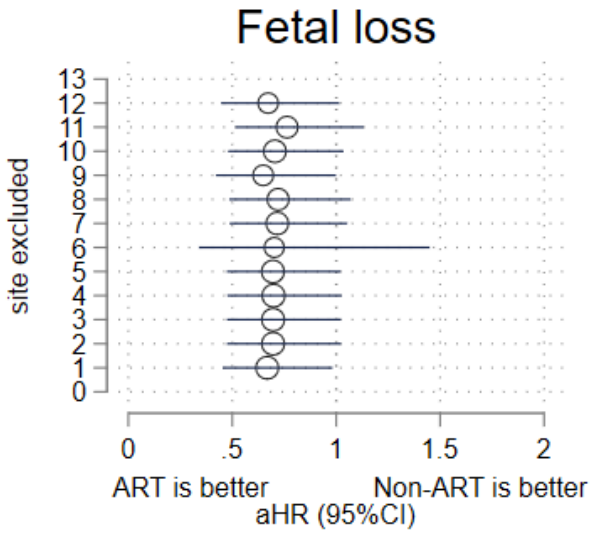
Sensitivity analysis- removing 1 cohort at time (1st trimester)

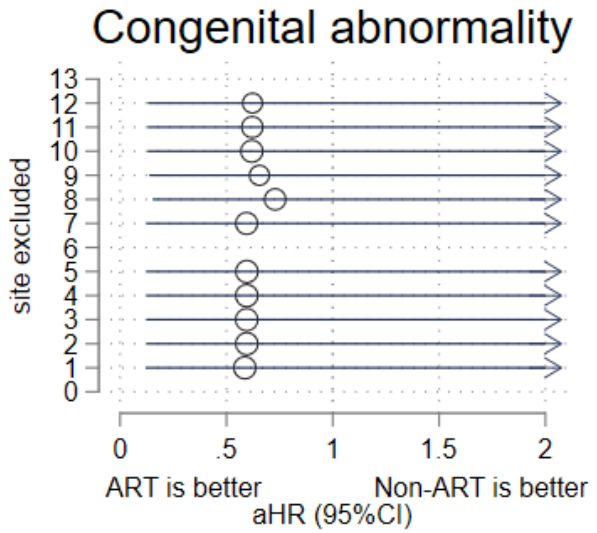
ABT vs non-ABT









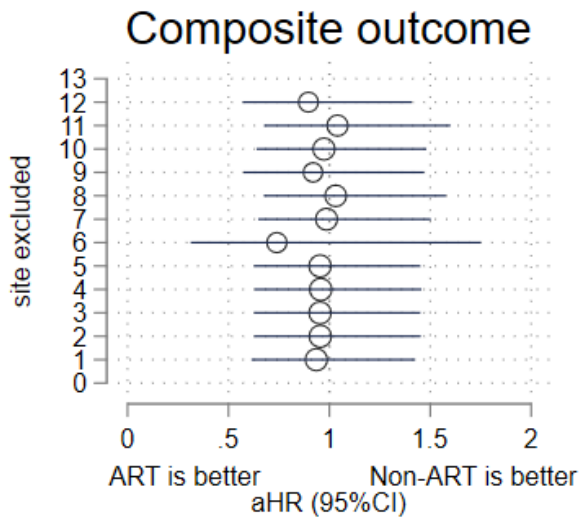


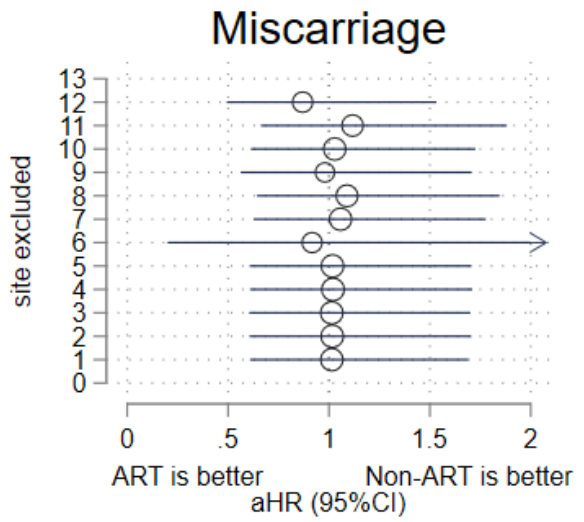
Study cohort legend:

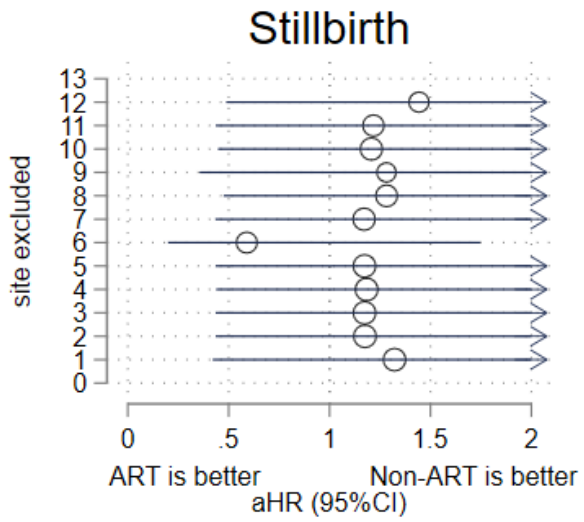
1: Rouamba, Burkina Faso
2: WHO TDR, Ghana
3: WHO TDR, Kenya
4: WHO TDR, Tanzania
5: WHO TDR, Uganda
6: McGready, Thailand
7: Tinto, Burkina Faso
8: Dellicour, Kenya
9: Mosha, Tanzania
10: Sevene, Mozambique
11: Rulisa, Rwanda
12: Manyando, Zambia.

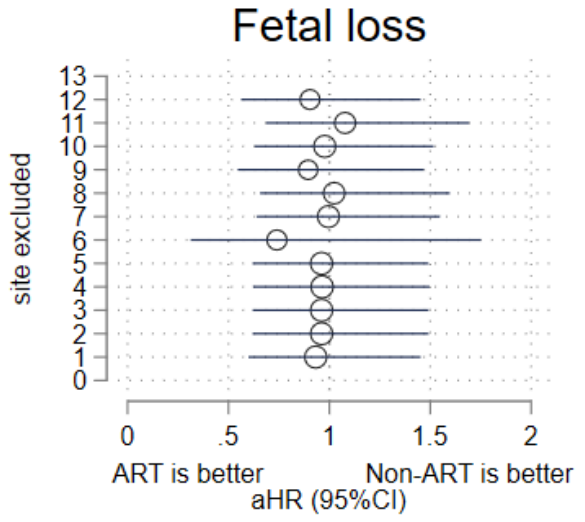
Sensitivity analysis- removing 1 cohort at time (embryo-sensitive)

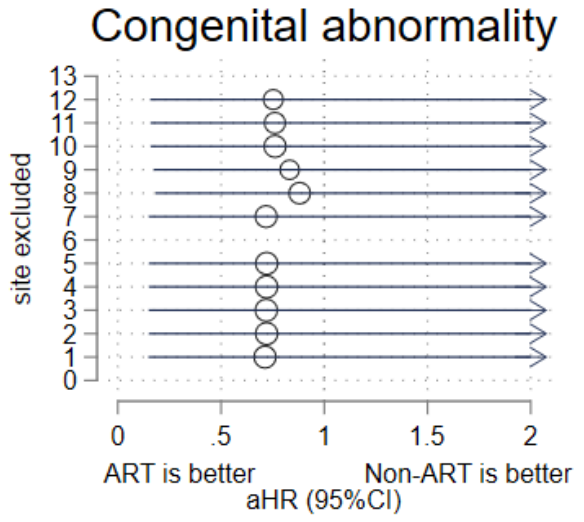
ABT vs non-ABT









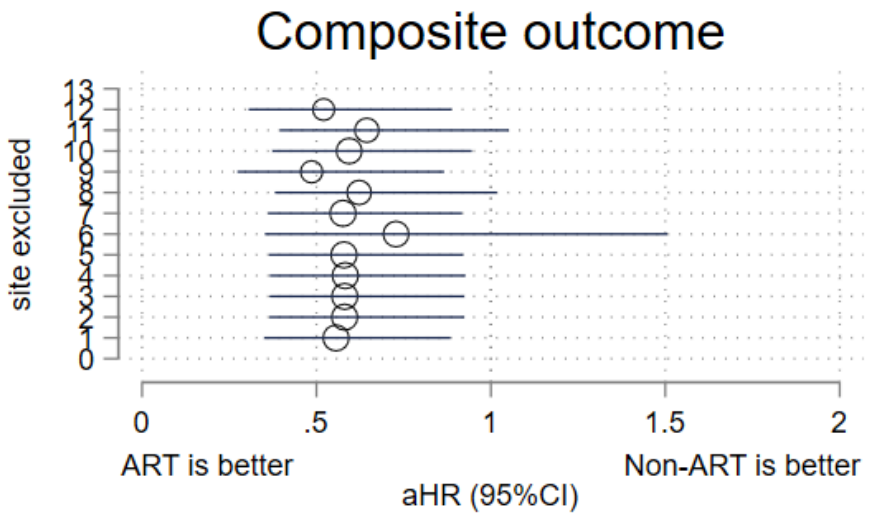


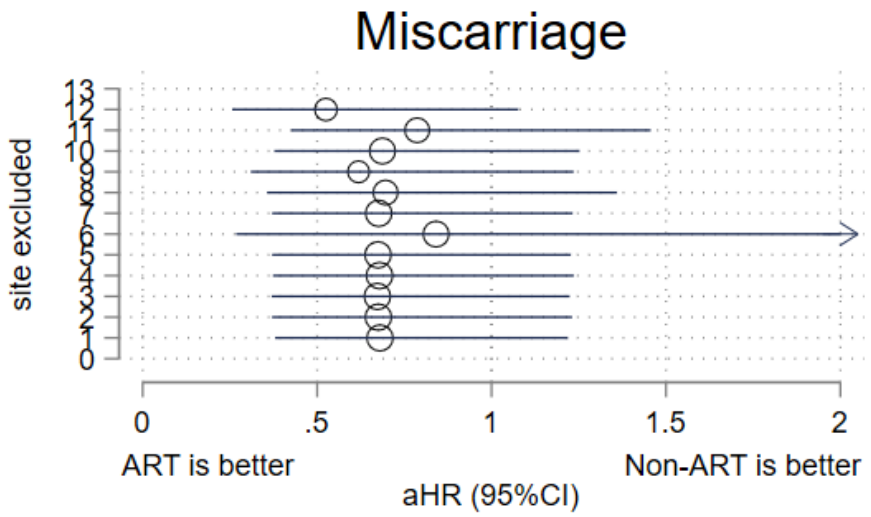
Study cohort legend:

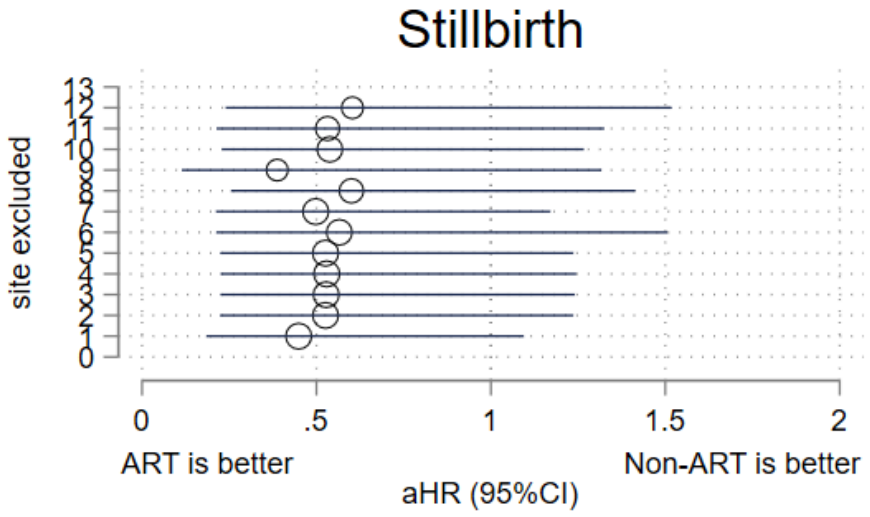
1: Rouamba, Burkina Faso
2: WHO TDR, Ghana
3: WHO TDR, Kenya
4: WHO TDR, Tanzania
5: WHO TDR, Uganda
6: McGready, Thailand
7: Tinto, Burkina Faso
8: Dellicour, Kenya
9: Mosha, Tanzania
10: Sevene, Mozambique
11: Rulisa, Rwanda
12: Manyando, Zambia.

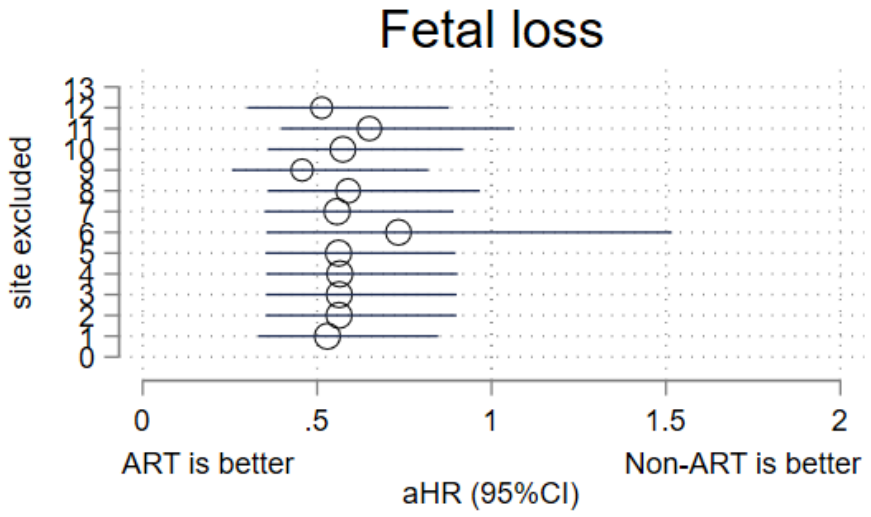
Sensitivity analysis- removing 1 cohort at time (1st trimester)

AL vs Quinine









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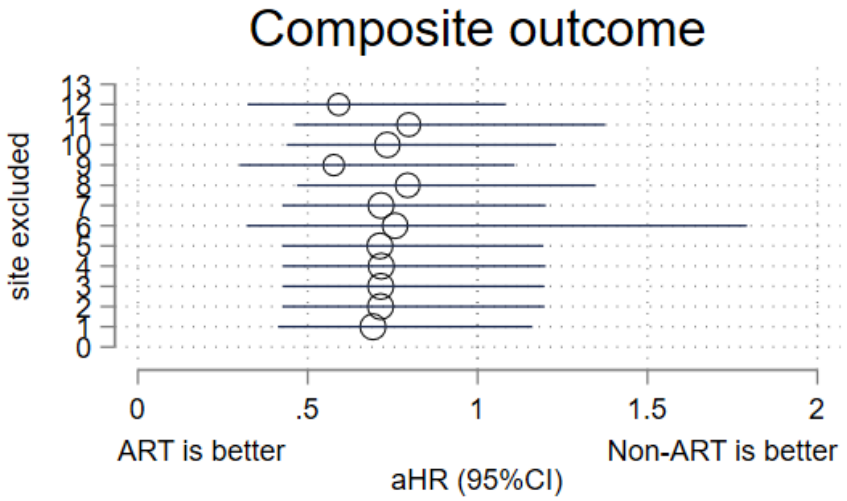
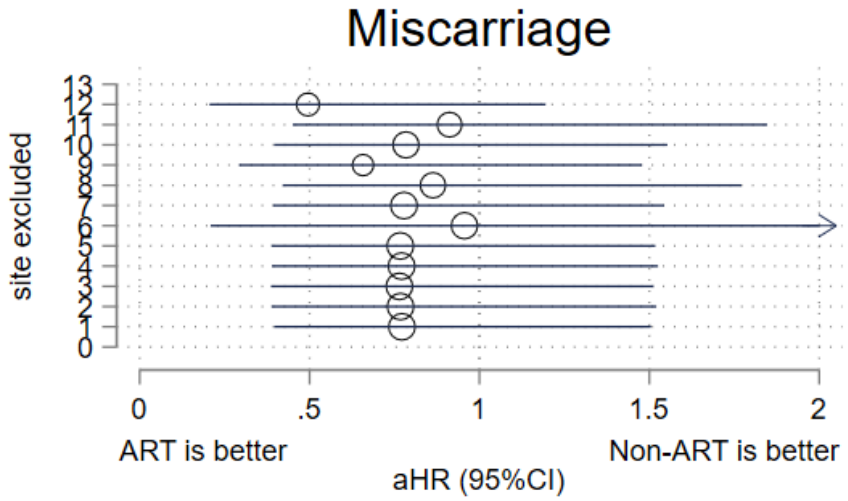
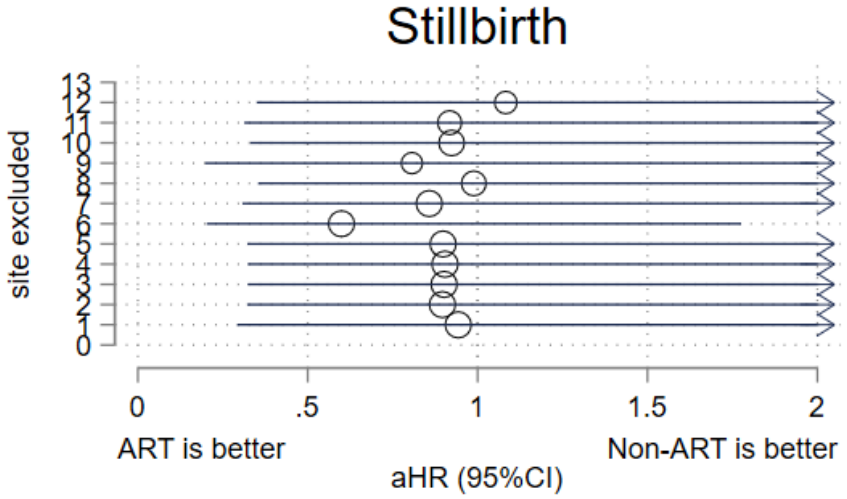
10: Sevene, Mozambique
11: Rulisa, Rwanda
12: Manyando, Zambia.

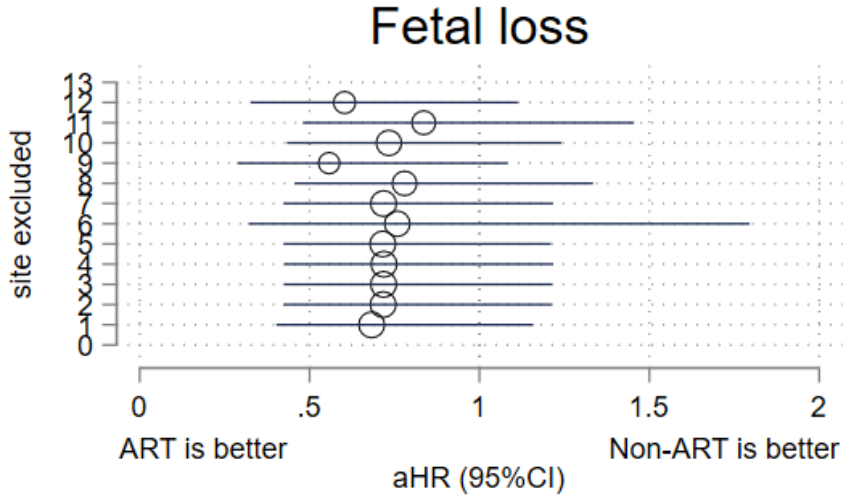
Sensitivity analysis- removing 1 cohort at time (embryo-sensitive)

AL vs Quinine









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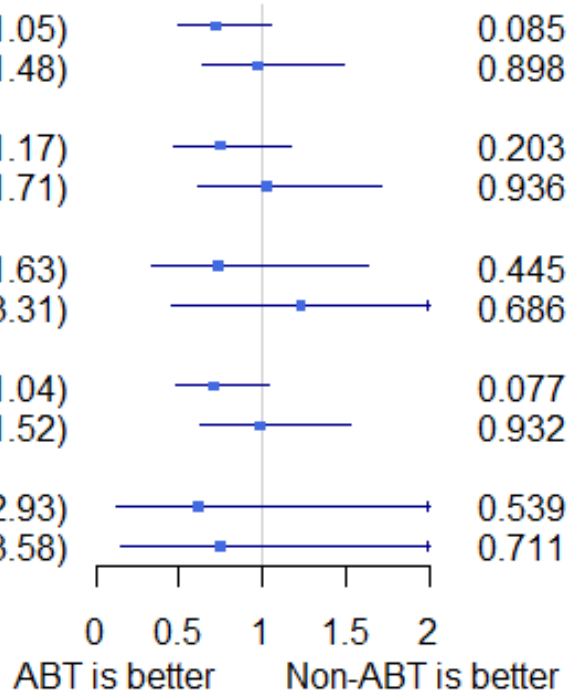
Sensitivity analysis- adjusting for additional variables with missing data

Outcome	Number ABT	Non-ABT	aHR (95%CI)	p-value	E-value
Composite outcome					
First trimester	42/737	96/1076	0.72 (0.50-1.05)	0.085	3.47
Embryo-sensitive period	37/584	60/823	0.97 (0.64-1.48)	0.898	2.54
Miscarriage					
First trimester	27/670	76/1072	0.75 (0.47-1.17)	0.203	3.69
Embryo-sensitive period	23/533	46/819	1.02 (0.61-1.71)	0.936	2.70
Stillbirth					
First trimester	13/646	12/745	0.73 (0.33-1.63)	0.445	5.58
Embryo-sensitive period	12/518	6/609	1.23 (0.45-3.31)	0.686	3.87
Fetal loss					
First trimester	40/737	88/1076	0.71 (0.48-1.04)	0.077	3.61
Embryo-sensitive period	35/584	52/823	0.98 (0.63-1.52)	0.932	2.58
Major congenital anomaly					
First trimester	2/737	8/1076	0.61 (0.13-2.93)	0.539	15.27
Embryo-sensitive period	2/584	8/823	0.74 (0.15-3.58)	0.711	12.56



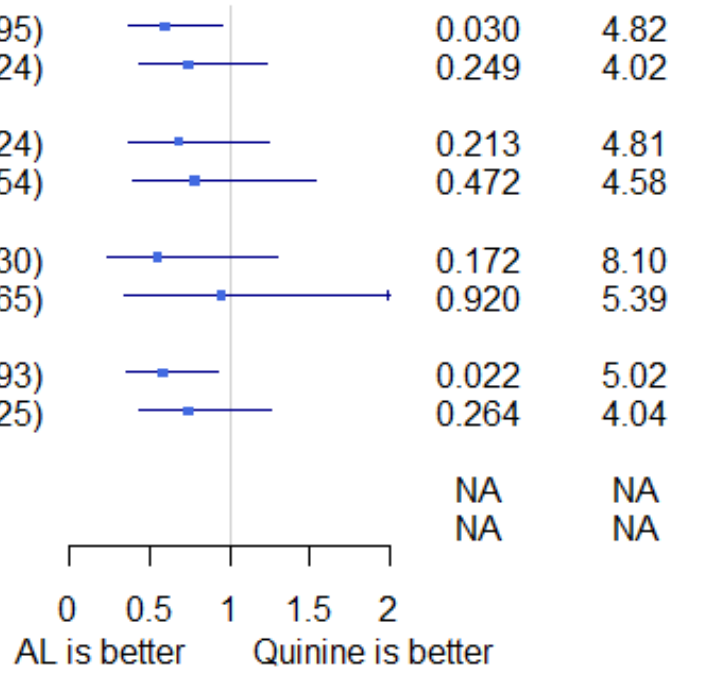
Adjusted for:

- age group (<20, 20s, 30s, >=40)
- gravidity group (1, 2, >=3)
- study year (2000–4, 2005–9, 2010–17)
- marital status
- smoking status
- previous miscarriage
- previous stillbirth

multiple imputation

Sensitivity analysis- adjusting for additional variables with missing data

Outcome	Number AL	Quinine	aHR (95%CI)	p-value	E-value
Composite outcome					
First trimester	25/525	84/917	0.60 (0.38-0.95)	0.030	4.82
Embryo-sensitive period	22/445	51/685	0.74 (0.44-1.24)	0.249	4.02
Miscarriage					
First trimester	15/465	68/915	0.68 (0.38-1.24)	0.213	4.81
Embryo-sensitive period	12/398	40/683	0.78 (0.39-1.54)	0.472	4.58
Stillbirth					
First trimester	10/488	12/592	0.55 (0.23-1.30)	0.172	8.10
Embryo-sensitive period	10/415	6/470	0.95 (0.34-2.65)	0.920	5.39
Fetal loss					
First trimester	25/525	80/917	0.58 (0.36-0.93)	0.022	5.02
Embryo-sensitive period	22/445	46/685	0.74 (0.44-1.25)	0.264	4.04
Major congenital anomaly					
First trimester	0/525	4/917	No events	NA	NA
Embryo-sensitive period	0/445	5/685	No events	NA	NA



Adjusted for:

- age group (<20, 20s, 30s, >=40)
- gravidity group (1, 2, >=3)
- study year (2000–4, 2005–9, 2010–17)
- marital status
- smoking status
- previous miscarriage
- previous stillbirth

multiple imputation

Sensitivity analysis- ABT vs non-ABT incl unconfirmed exposures

	Embryo-sensitive period (6-12 weeks gestation inclusive)					First trimester (2-13 weeks gestation inclusive)				
	ABT	non-ABT	aHR (95%CI)	p-value	E-value	ABT	non-ABT	aHR (95%CI)	p-value	E-value
Composite	54/770	64/915	1.06 (0.73-1.54)	0.753	2.11	69/1023	100/1230	0.84 (0.61-1.16)	0.283	2.70
Miscarriage	39/690	47/899	1.29 (0.83-2.01)	0.251	1.72	52/914	77/1211	0.97 (0.67-1.41)	0.872	2.39
Stillbirth	13/687	9/697	0.80 (0.34-1.91)	0.622	5.40	15/907	15/892	0.61 (0.29-1.27)	0.184	6.38
Fetal loss	52/770	56/915	1.08 (0.73-1.59)	0.711	2.11	67/1023	92/1230	0.83 (0.60-1.15)	0.265	2.77
Major congenital anomalies	2/770	8/915	0.59 (0.12-2.85)	0.509	16.20	2/1023	8/1230	0.47 (0.10-2.28)	0.348	20.42

1023 ABT: 917 ACT (788 AL, 42 ASAQ, 58 ASMQ, 26 DP, 3 artesunate-atovaquone-proguanil), 95 AS/AC, 8 parenteral, 3 artemether

1230 non-ABT: 1043 oral quinine (841 quinine monotherapy, 202 quinine+clindamycin), 32 parenteral quinine, 147 chloroquine, 8 amodiaquine,1 atovaquone-proguanil, 1 mefloquine, 1 quinine+mefloquine, 2 details not available